Implementing principles of Quality by Design (QbD) in validation context

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Université de Liège

Overview

1. Introduction
2. Quality-by-Design approach:
   Development and optimization step
3. Tolerance interval as a predictive approach:
   Validation step
4. Quality-by-Design: a tool for an Intergration between optimization and validation phases
5. Conclusions

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Introduction

QbD within regulatory context

***Quality-by-Design* for process**

- Patient requirements
- Process design and development
- Risk assessment & process design space definition
- Control strategy

Continuous improvement

Knowledge repository

Analytical Quality-by-Design

- Method performance requirements (ATP)
- Method development
- Risk assessment & analytical method design space definition
- Analytical method control strategy

P. Borman et al., Pharm. Technol., 2007

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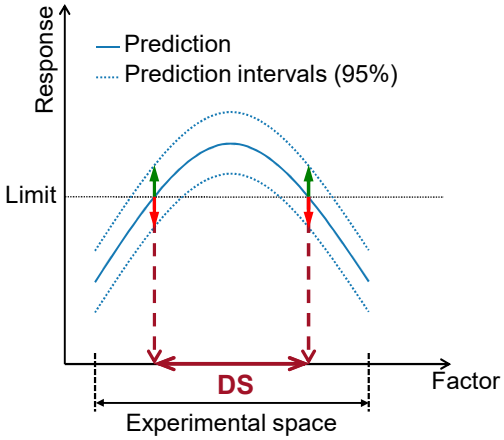
Method optimization: Design Space

DoE-DS methodology



- Design of Experiments
- *CMP*
- *CQA*
- Responses
- Statistic model
- Uncertainty of the model

Assessment of the risk linked to the "*qualitative performances*" of the method

$$\boldsymbol{DS} = \{\mathbf{x}_0 \in \chi | \boldsymbol{E}_\theta[\boldsymbol{P}(\mathbf{CQAs} \in \boldsymbol{\Lambda}) | \mathbf{X} = \mathbf{x}_0, \theta] \geq \pi\}$$

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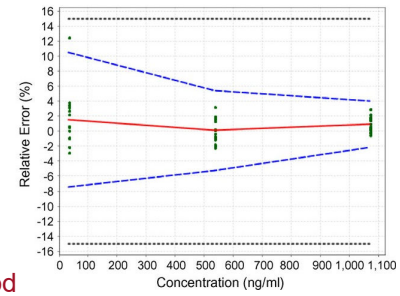
Introduction

Accuracy Profile

- *β*-expectation tolerance intervals

Ph. Hubert et al., J. Pharm. Biomed. Anal., 2004

- Predictive decisional tool
  - Total error
  - Risk *a priori*
  - Acceptance limits - ATP



Assessment of the risk linked to the "*quantitative performances*" of the method

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Quality-by-Design approach

Case study: Impurities determination (stability study)

Method: LC-ESI(+)-MS
- *m/z (P4FX98)*: 116
- *m/z (P4NX99)*: 117
- heteroatoms / structural analogous

Context: Co-eluted unknown impurities (C1, C2 et C3) from complex matrix, recorded at same m/z ratio

"Improvement of a stability-indicating method by Quality-by-Design versus Quality-by-Testing: A case of a learning process"

***C. Hubert** et al., Journal of Pharmaceutical and Biomedical Analysis, 2014.*

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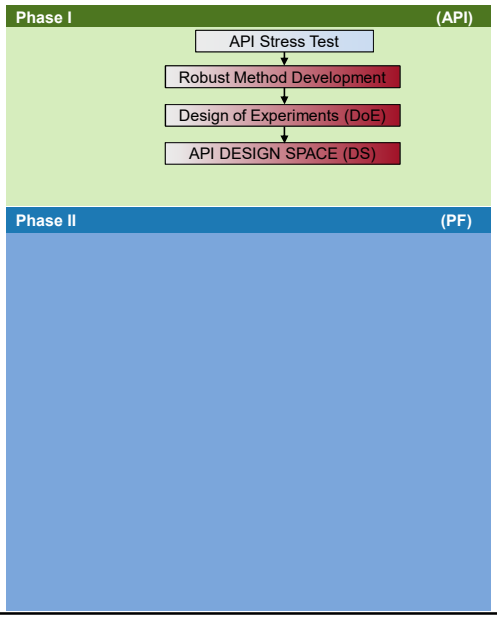
Quality-by-Design approach

Phase I:

Selectivity between API and known impurities?



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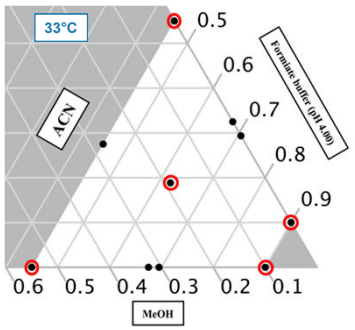
Quality-by-Design approach

Phase I: API and known impurities (stress test)

- Fixed conditions:
  - pH = 4.0
  - 2 C_{18} columns
- DoE studied condition:
  - $\%_{O.M.}$ (buffer/ACN/MeOH)
  - Temperature (22°C à 44°C)

➔ Mixture D-optimal design
- 20 points (n = 22)
- 3 days



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Quality-by-Design approach

Phase I: API and known impurities (stress test)

Reponses: $T_{r,B}$, $T_{r,A}$ et $T_{r,E}$

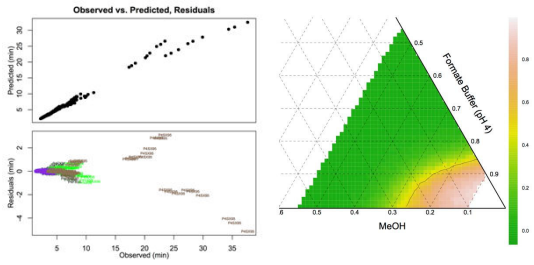
Model:

$$Y = \beta_1 \times MeOH + \beta_2 \times ACN + \beta_3 \times Buffer + \beta_4 \times T + \beta_5 \times T^2 + \beta_6 \times T \times MeOH + \beta_7 \times T \times ACN + \beta_8 \times T \times Buffer + \beta_9 \times MeOH \times ACN + \beta_{10} \times MeOH \times Buffer + \beta_{11} \times ACN \times Buffer + E$$

CQAs: $S_{P4FX98\text{-}P4NX99} > 0.2$ min $t_{B(P4MX01)} > t_{E(impurities)}$

Results:

- ODS-3
- 22°C – 30°C
- π : 0.65 – 0.85



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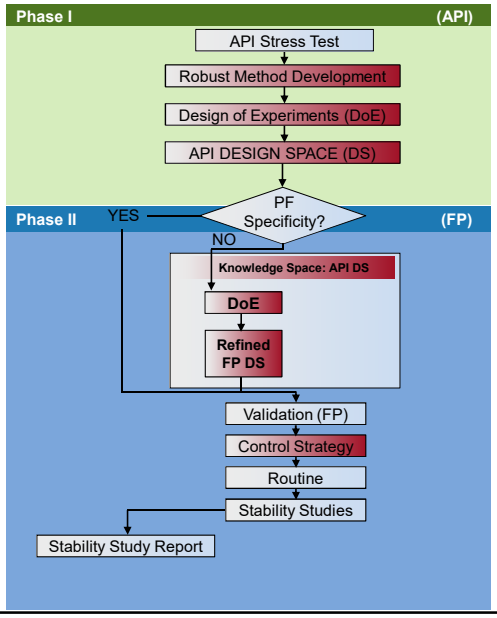
Quality-by-Design approach

Phase I:

Selectivity between API and known impurities ✔

Phase II:

Selectivity guaranteed within the finished product?



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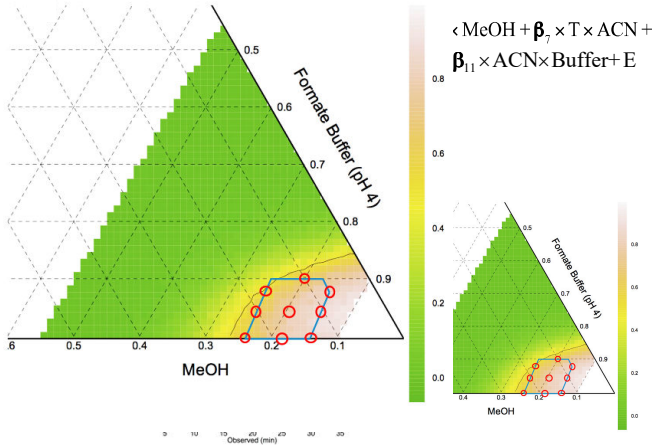
Quality-by-Design approach

Phase II: Stability-indicating method

Reponses:

Model: $Y = \beta_1 \times$ ... $\beta_8 \times$ ... $\times MeOH + \beta_7 \times T \times ACN + \beta_{11} \times ACN \times Buffer + E$

CQAs:



Results:

- ODS-3
- 22°C – 30°C
- π : 0.65 – 0.

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Quality-by-Design approach

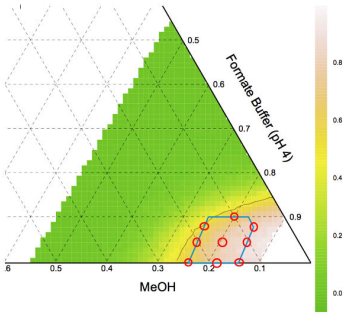
Phase II: Stability-indicating method

Fixed conditions (**aged matrix**) :

- Inertsil ODS-3 2.1x150 mm (5µm)
- pH: 4.0
- Temperature: 25°C

➔ Mixture D-optimal design

- 9 conditions (n = 11)
- 1 day



$$Y = \beta_1 \times MeOH + \beta_2 \times ACN + \beta_3 \times Buffer + \beta_4 \times MeOH \times ACN + \beta_5 \times MeOH \times Buffer + \beta_6 \times ACN \times Buffer + E$$

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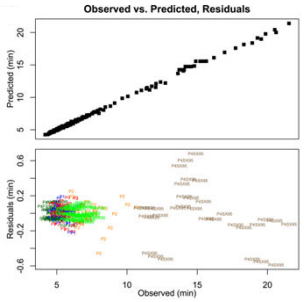
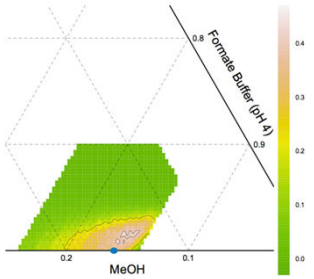
Quality-by-Design approach

Phase II: Stability-indicating method

Reponses: $T_{r,B}$, $T_{r,A}$ et $T_{r,E}$

Results:





CQAs:

$S_{P4FX98-P4NX99}$ > 0.2 min
$t_{B(P4MX01)} > t_{E(impuretés)}$

$S_{C1-P4NX99}$ > 0.2 min
$S_{P4NX99-C2}$ > 0.2 min

$S_{P4FX98-C3}$ > 0.2 min
$t_{E(P4SX95)}$ < 22 min

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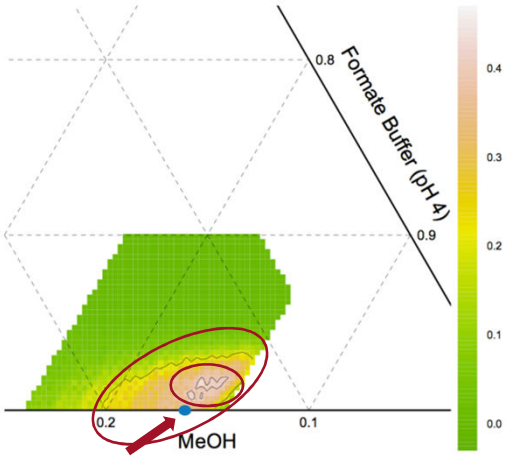
Quality-by-Design approach

Phase II: Stability-indicating method

DS : π_{min} = 0.3
= 0.45

Binary mixture selected



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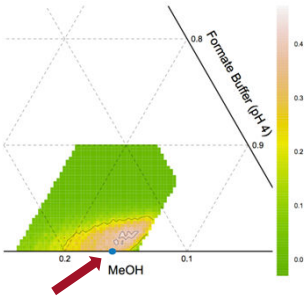
Quality-by-Design approach

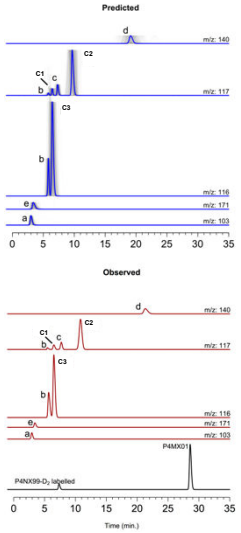
Phase II: Stability-indicating method

Selected working conditions:

- Inertsil ODS-3 2.1x150 mm (5 µm)
- MeOH / NH_4Ac pH: 4.0 (16/84, v/v)
- Temperature: 25°C

$R^2 = 0.998$





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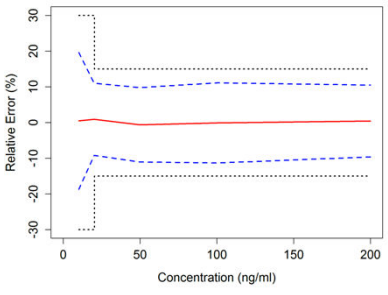
Quality-by-Design approach

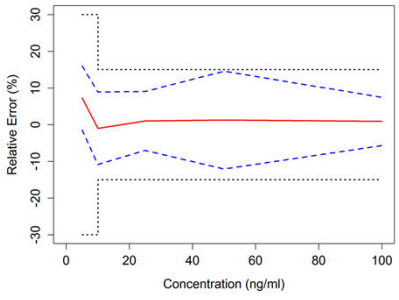
Validation

P4FX98



Linear regression

P4NX99



Linear regression through 0

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Method validation: quantitative risk assessment

Validation objective:

Management of the risk associated to the results

Tolerance interval as a predictive approach

Pre-study versus in-study

"Using tolerance intervals in pre-study validation of analytical methods to predict in-study results: The fit-for-future-purpose concept"

***C. Hubert** et al., Journal of Chromatography A, 2007.*

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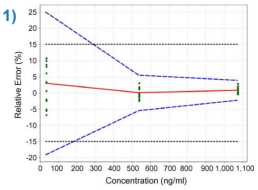
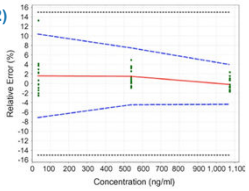
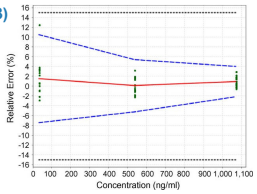
Pre-study versus in-study

Levonorgestrel (proportion (β): 95%)

Method		Calibration model (within matrix)	Concentration (ng/mL)	Lower limit of β-expectation interval (%)	Upper limit of β-expectation interval (%)
LC-UV	1	Linear regression	30	- 19,1	25,2
			500	- 5,4	5,6
	2	Linear regression after Log transformation	30	- 7,2	10,4
			500	- 4,5	7,5
	3	Weighted (1/X) linear regression	30	- 7,5	10,5
			500	- 5,2	5,4

1) 

2) 

3) 

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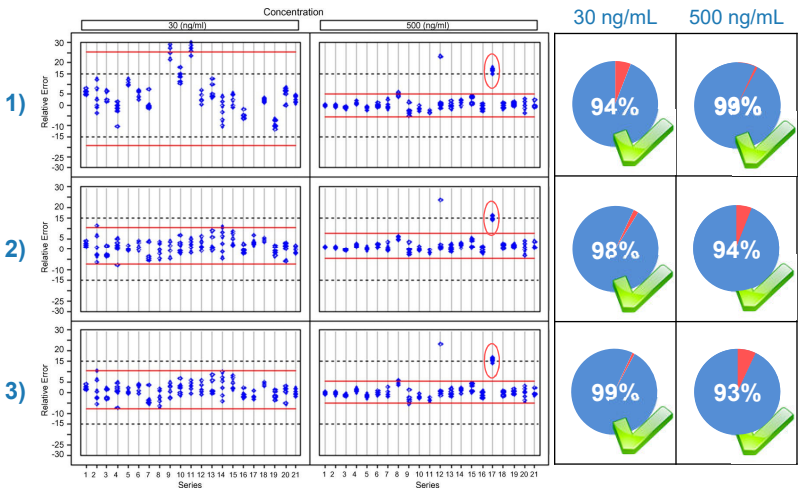
Pre-study versus in-study

Routine: 252 QC (*m* = 21; *n* = 6 ; *k* = 2)



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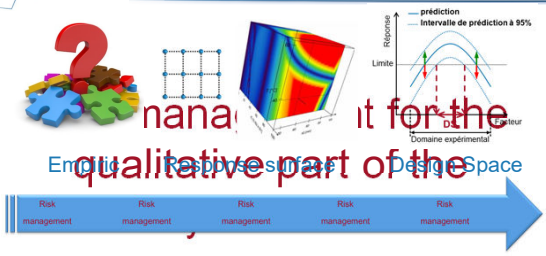
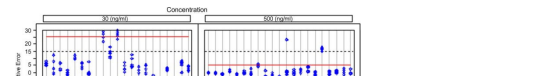
Towards a full integration of optimization and validation phases



nana t for the qualitative part of the

Empiric Response surface Design Space



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Quantitative QbD strategy

Design Space : a knowledge space

Risk management of quantitative performance of the analytical procedure throughout an entire experimental domain?

"Towards a full integration of optimization and validation phases: An Analytical-Quality-by-Design approach"

***C. Hubert** et al., Journal of Chromatography A, 2015.*

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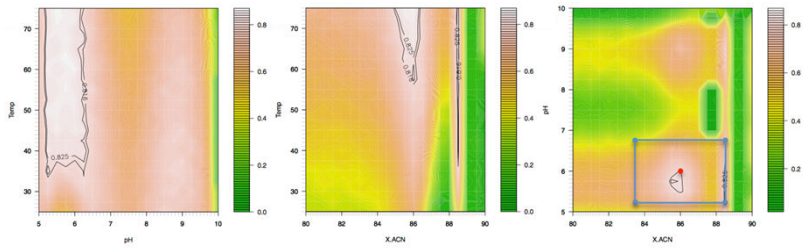
Quantitative QbD strategy

Working space

Glucosamine / galactosamine in human plasma (SPE-UHPLC-MS/MS)

- *CMPs* : *ACN*, *pH*, *T*.
- Acquity BEH Amide 2.1x100 mm (1.7 µm)
- *Custom central composite* Design (n = 15)
- CQAs: $S_{all\ compounds}$ > 0.2 min et T_{run} < 30 min.

ACN = 88.5% *pH* = 5.75 *T* = 50°C



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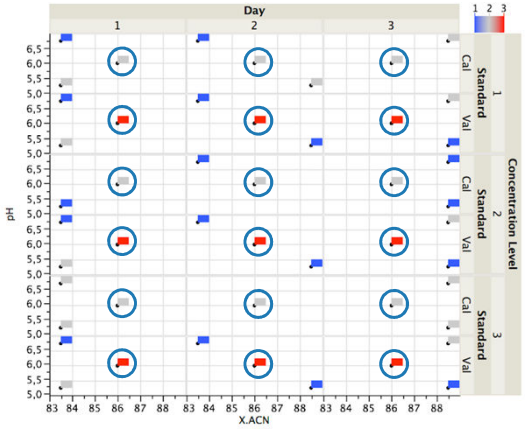
Quantitative QbD strategy

Working space

Validation design (T = 50°C) :



Reference point: 86% ACN / pH = 6 / 50°C

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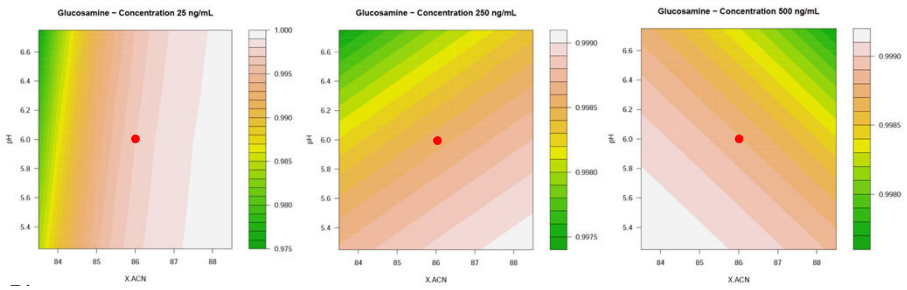
Quantitative QbD strategy

Probability of success

$$\mathbf{Y} = \beta_0 + \beta_1 \times \text{pH} + \beta_2 \times \text{ACN} + \beta_3 \times \text{concentration} + \beta_4 \times \text{pH} \times \text{ACN} + \beta_5 \times \text{concentration} \times \text{pH} + \beta_6 \times \text{concentration} \times \text{ACN} + \varepsilon$$

Glucosamine (25 - 500 ng/mL) :



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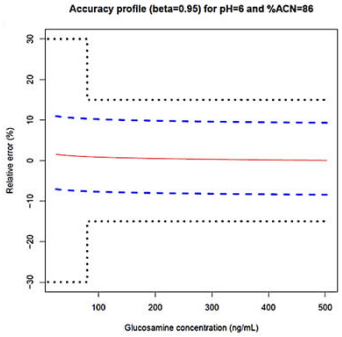
Quantitative QbD strategy

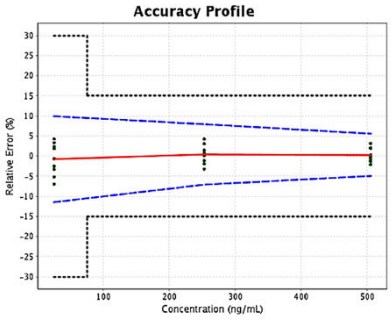
Validation of the working space

Glucosamine (at reference point)

Validation considering the entire working space (χ)



Validation considering a single set of experimental condition



Weighted (1/X) linear regression

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Conclusions

Quality-by-Design:

Management of the risk linked to the qualitative part of the analytical method

Usefulness of the DoE-DS approach

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Conclusions

Validation:

Management of the risk linked to the quantitative part of the analytical method

Tolerance interval is a good predictive tool

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Conclusions

Full integration of optimization and validation phases:

Risk management of the quantitative part of the analytical method throughout a working space where qualitative performance is achieved

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Acknowledgments

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- Philippe Hubert, Prof.
- Eric Ziémons, Ph. D.
- All members of LAC
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- Eric Rozet, Ph. D. (Arlenda)

Thanks for your attention

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